US005902803A

United States Patent [19]

Aloup et al.

[11] Patent Number: 5,902,803

[45] Date of Patent: May 11, 1999

[54] **5H,10H-IMIDAZO[1,2-A]INDENO[1,2-E] PYRAZIN-4-ONE DERIVATIVES, PREPARATION THEREOF, AND DRUGS CONTAINING SAID DERIVATIVES**

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[21] Appl. No.: **08/930,967**

[22] PCT Filed: **Apr. 2, 1996**

[86] PCT No.: **PCT/FR96/00496**

§ 371 Date: **Oct. 3, 1997**

§ 102(e) Date: **Oct. 3, 1997**

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PCT Pub. Date: **Oct. 10, 1996**

[30] **Foreign Application Priority Data**

Apr. 5, 1995 [FR] France 95/04013

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[52] **U.S. Cl.** **514/81**; 514/250; 544/243; 544/343; 548/111; 548/334.5

[58] **Field of Search** 544/343, 243; 514/81, 250

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Primary Examiner—Mark L. Berch

Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

[57] **ABSTRACT**

Compounds of formula (I), wherein R is a hydrogen atom or a carboxy, alkoxycarbonyl, —CO—NR_4R_5, —PO_3H_2 or —CH_2OH radical, and R_1 is an -alk-NH_2, -alk-NH—CO—R_3, -alk-$COOR_4$, -alk-CO—NR_5R_6 or —CO—NH—R_7 radical. The compounds of formula (I) have valuable pharmacological properties and are antagonists of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor also known as the quisqualate receptor. Furthermore, the compounds of formula (I) are non-competitive antagonists of the N-methyl-D-aspartame (NMDA) receptor and more specifically are ligands for NMDA receptor glycine modulator sites.

7 Claims, No Drawings

The enantiomers of the compounds of formula (I) can be obtained by resolution of the racemates, for example by chromatography on a chiral column, according to W. H. Pirckle et al., Asymmetric Synthesis, vol. 1, Academic Press (1983), or by synthesis from chiral precursors.

The diastereoisomers of the compounds of formula (I) can be separated by the usual known methods, for example by crystallization or chromatography.

The compounds of formula (I) containing a basic residue can optionally be converted to addition salts with an inorganic or organic acid by the action of such an acid in an organic solvent such as an alcohol, a ketone, an ether or a chlorinated solvent.

The compounds of formula (I) containing an acid residue can optionally be converted to metal salts or to addition salts with nitrogenous bases according to methods known per se. These salts can be obtained by the action of a metal base (alkali metal or alkaline-earth metal base, for example), ammonia, an amine or a salt of an amine on a compound of formula (I), in a solvent. The salt formed is separated by the usual methods.

These salts also form part of the invention.

There may be mentioned, as examples of pharmaceutically acceptable salts, the addition salts with inorganic or organic acids (such as acetate, propionate, succinate, benzoate, fumarate, maleate, oxalate, methanesulphonate, isethionate, theophyllinacetate, salicylate, methylenebis(β-hydroxynaphthoate), hydrochloride, sulphate, nitrate and phosphate), the salts with alkali metals (sodium, potassium or lithium) or with alkaline-earth metals (calcium or magnesium), the ammonium salt or the salts of nitrogenous bases (ethanolamine, trimethylamine, methylamine, benzylamine, N-benzyl-β-phenethylamine, choline, arginine, leucine, lysine or N-methylglucamine).

The compounds of formula (I) exhibit advantageous pharmacological properties. These compounds are antagonists of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, also known under the name of the quisqualate receptor.

Moreover, the compounds of formula (I) are non-competitive antagonists of the N-methyl-D-aspartate (NMDA) receptor and, more particularly, they are ligands for the glycine-modulatory sites of the NMDA receptor.

These compounds are thus useful for treating or preventing all ischaemias (such as focal or global ischaemia) resulting from cerebrovascular accidents such as thromboembolic and haemorrhagic stroke, a cardiac arrest, arterial hypotension, a heart, vascular or pulmonary surgical operation or severe hypoglycaemia. They are also useful in the treatment of effects due to anoxia, whether perinatal or resulting from drowning, high pressure or cerebrospinal lesions. These compounds can also be used for treating or preventing the development of neurodegenerative diseases, Huntington's chorea, Alzheimer's disease and other dementias, amyotrophic lateral sclerosis or other motoneuron diseases, olivopontocerebellar atrophy and Parkinson's disease. These compounds can also be used with respect to epileptogenic and/or convulsive symptoms, for the treatment of cerebral or spinal traumas, of traumas related to degeneration of the inner ear (R. Pujol et al., Neuroreport, 3, 299–302 (1992)) or of the retina (J. L. Monsinger et al., Exp. Neurol., 113, 10–17 (1991)), of tinnitus, of anxiety (Kehne et al., Eur. J. Pharmacol., 193, 283 (1991)), of depression (Trullas et al., Eur. J. Pharmacol., 185, 1 (1990)), of schizophrenia (Reynolds, TIPS, 13, 116 (1992)), of Tourette's syndrome, of hepatic encephalopathies, of sleep disorders, of attention deficit disorders or of disorders of hormonal conditions (excess secretion of HG or HL or secretion of corticosterone), as analgesics (Dickenson et al., Neurosc. Letters, 121, 263 (1991)), antiinflammatories (Sluta et al., Neurosci. Letters, 149, 99–102 (1993)), antianorexics (Sorrels et al., Brain Res., 572, 265 (1992)), antimigraines and antiemetics, and for treating poisonings by neurotoxins or other agonist substances of the NMDA or AMPA receptor, and neurological disorders associated with viral diseases such as viral meningitides and encephalitides, AIDS (Lipton et al., Neuron, 7, 111 (1991)), rabies, measles and tetanus (Bagetta et al., Br. J. Pharmacol., 101, 776 (1990)). These compounds are also useful for preventing, tolerating and depending on symptoms of withdrawal from drugs or from alcohol and inhibiting addiction to and dependence on opiates, barbiturates, amphetamine and benzodiazepines. They can also be used in the treatment of deficiencies related to mitochondrial anomalies such as mitochondrial myopathy, Leber's syndrome, Wernicke's encephalopathy, Rett's syndrome, homocysteinaemia, hyperprolinaemia, hydroxybutiricaminoaciduria, saturnine encephalopathy (chronic lead poisoning) and sulphite oxidase deficiency.

The affinity of the compounds of formula (I) with respect to the AMPA receptor was determined by studying the antagonism of the specific binding of [^{3}H]-AMPA on rat cerebral cortex membranes (Honoré et al., Neuroscience Letters, 54, 27 (1985)). The [^{3}H]-AMPA is incubated in the presence of 0.2 mg of proteins at 4° C. for 30 minutes in 10 mM KH_2PO_4, 100 mM KSCN, pH 7.5 buffer. The non-specific binding is determined in the presence of 1 mM L-glutamate. The bonded radioactivity is separated by filtration on Pharmacia filters (Printed Filtermate A). The inhibiting activity of these products is less than or equal to 100 μM.

The affinity of the compounds of formula (I) for the glycine site linked to the NMDA receptor was determined by studying the antagonism of the specific binding of [^{3}H]-DCKA on rat cerebral cortex membranes according to the method described by T. Canton et al., J. Pharm. Pharmacol., 44, 812 (1992). The [^{3}H]-DCKA (20 nM) is incubated in the presence of 0.1 mg of proteins at 4° C. for 30 minutes in 50 mM, pH 7.5, HEPES buffer. The non-specific binding is determined in the presence of 1 mM glycine. The bonded radioactivity is separated by filtration on Whatman GF/B filters. The inhibiting activity of these products is less than or equal to 100 μM.

The compounds of formula (I) have a low toxicity. Their LD_{50} in mice is greater than 50 mg/kg by the IP route.

The preferred compounds of formula (I) are those in which R represents a hydrogen atom or a carboxy radical, R_1 represents an -alk-NH—CO—R_3, -alk-$COOR_4$, -alk-CO—NR_5R_6 or —CO—NH—R_7 radical, R_3 represents an alkyl or —NR_8R_8 radical, R_4 represents a hydrogen atom, R_5 represents a hydrogen atom, R_6 represents an alkyl radical and R_7 represents a phenylalkyl or -alk-$COOR_4$ radical.

Among the latter are preferred the following compounds:

(4,5-dihydro-4-oxo-10H-imidazo[1,2-a]indeno[1,2-e]pyrazin-9-yl)acetic acid,

N-methyl-2-(4,5-dihydro-4-oxo-10H-imidazo[1,2-a]indeno[1,2-e]pyrazin-9-yl)acetamide,

N-[(4,5-dihydro-4-oxo-10H-imidazo[1,2-a]indeno[1,2-e]pyrazin-9-yl)methyl]acetamide,

9-[(3-methylureido)methyl]-5H,10H-imidazo[1,2-a]indeno[1,2-e]pyrazin-4-one,

N-methyl-[4,5-dihydro-4-oxo-10H-imidazo[1,2-a]indeno[1,2-e]pyrazin-8-yl]acetamide,

8-N-methylcarboxamidomethyl-4,5-dihydro-4-oxo-10H-imidazo[1,2-a]indeno[1,2-e]pyrazin-2-carboxylic acid,

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Glycine-site NMDA receptor antagonists: an update. Kulagowski, Janusz J. Merck Sharp Dohme Res. Lab., Neurosci. Res. Centre, Harlow, UK. Expert Opinion on Therapeutic Patents (1996), 6(10), 1069-1079. Publisher: Ashley Publications, CODEN: EOTPEG ISSN: 1354-3776. Journal; General Review written in English. CAN 125:264799 AN 1996:630964 CAPLUS

Abstract

A review with 66 refs. Animal models predict that antagonists acting at the glycine-site of the N-methyl-D-aspartate (NMDA) receptor have potential in the treatment of stroke, head injury, epilepsy and schizophrenia, and may offer considerable therapeutic advantage over other classes of NMDA antagonists. Recent developments, particularly in the patent literature, are reviewed for the period since June 1995. The available data on three compds. believed to be in clin. development, namely GV150526A (Glaxo Wellcome), ACEA 1021 (CoCensys/Ciba-Geigy) and ZD9379 (Zeneca), are highlighted. Other compd. classes discussed include quinoxaline-2,3-diones and analogs, imidazolopyrazinones, pyridone derivs., benzazepinediones, 2-carboxyindoles, pyridazinoquinolines and misc. other compds.

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Evaluation of memantine for neuroprotection in dementia. Jain, Kewal K. Jain PharmaBiotech, Basel, Switz. Expert Opinion on Investigational Drugs (2000), 9(6), 1397-1406. Publisher: Ashley Publications Ltd., CODEN: EOIDER ISSN: 1354-3784. Journal; General Review written in English. CAN 133:129433 AN 2000:411031 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

Abstract

A review with 35 refs. Memantine, a non-competitive NMDA antagonist, has been approved for use in the treatment of dementia in Germany for over ten years. The rationale for use is excitotoxicity as a pathomechanism of neurodegenerative disorders. Memantine acts as a neuroprotective agent against this pathomechanism, which is also implicated in vascular dementia. HIV-1 proteins Tat and gp120 have been implicated in the pathogenesis of dementia assocd. with HIV infection and the neurotoxicity caused by HIV-1 proteins can be blocked completely by memantine. Memantine has been investigated extensively in animal studies and following this, its efficacy and safety has been established and confirmed by clin. experience in humans. It exhibits none of the undesirable effects assocd. with competitive NMDA antagonists such as dizocilpine. The efficacy of memantine in a variety of dementias has been shown in clin. trials. Memantine is considered to be a promising neuroprotective drug for the treatment of dementias, particularly Alzheimer's disease for which there is no neuroprotective therapy available currently. It can be combined with acetylcholinesterase inhibitors which are the mainstay of current symptomatic treatment of Alzheimer's disease. Memantine has a therapeutic potential in numerous CNS disorders besides dementias which include stroke, CNS trauma, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), epilepsy, drug dependence and chronic pain. If memantine is approved by the FDA for some of these indications by the year 2005, it can become a blockbuster drug by crossing the US$1 billion mark in annual sales.

US006197830B1

(12) **United States Patent**
Frome

(10) **Patent No.: US 6,197,830 B1**
(45) **Date of Patent: Mar. 6, 2001**

(54) **METHOD FOR ACHIEVING RELIEF FROM SYMPATHETICALLY MEDIATED PAIN**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/531,760**

(22) Filed: **Sep. 22, 1995**

(51) **Int. Cl.**[7] A61K 31/135; A61K 31/137; A61K 31/395; A61K 31/485

(52) **U.S. Cl.** **514/654**; 514/647; 514/289; 514/183; 514/450; 514/654

(58) **Field of Search** 514/183, 289, 514/647, 654, 450

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Primary Examiner—Phyllis G. Spivack
(74) *Attorney, Agent, or Firm*—Gray Cary Ware & Freidenrich LLP

(57) **ABSTRACT**

A method is presented whereby sympathetically mediated pain relief is achieved through the periodic topical administration of compositions comprising tricyclic antipressants mixed with one or more topical bases, and applying to the skin above areas affected by pain.

Dextromethorphan or ketamine from the pharmacological class of NMDA receptor antagonists is optionally combined.

The topical vehicle bases which are needed to drive the pharmacological agents through the dermis into the subcutaneous tissue, either singly or in combinations, may be selected from the group comprising cocoa butter, aloe vera gel, aquafor, petroleum jelly, lecithin, and standard cold cream.

9 Claims, No Drawings

2. Topical local anesthetics or salicylates: Pain relief occurs in fewer than 25% of the SMP patients. Even then, only half of the pain is relieved.

3. Capsaicin (Cayenne Pepper Extract): This agent applied topically results in an initial burning sensation that discourages the SMP patient from its further use. It provides substantial pain relief for only a small number of SMP patients and then not until after one week of repetitive use.

V. Miscellaneous Other Methods: Although these techniques are occasionally successful, pain relief results in SMP is considered minimal. These methods include, but are not limited to, guided imagery techniques, acupuncture, hypnosis, physical therapy, and biofeedback.

OBJECTS AND ADVANTAGES

The object of the invention is to provide a process for the preparation of a composition that results in a relatively simple topical method of pain relief in patients with all types of pain, especially sympathetically mediated pain (SMP) or pain due to nerve damage, including peripheral neuropathies.

It is another object of the invention to provide a method of preparation of a composition that results in pain relief in SMP patients after the application of topical substances.

An additional object of the invention is to provide a composition for pain relief which will last longer than two hours. A further object of the invention is to provide a composition for pain relief which will last longer than 2 hours and which can be self-administered.

A still further object of the invention is to provide a method of preparation of this type of topical self administered pain relief utilizing non toxic agents with minimal side effects.

A yet further object of the invention to provide a method of preparation of this type of non-toxic, minimal side effect, topical medication for the treatment of patients with pain, especially nerve injury pain or sympathetically mediated pain, which is non-addictive and non-habit forming.

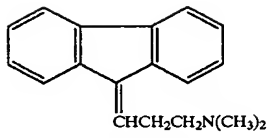
Still further objects and advantages will become apparent through a consideration of the ensuing description.

PREFERRED EMBODIMENT: DESCRIPTION AND OPERATION

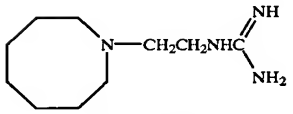
The present invention relates to the methods of preparation of the compositions used as topical regional treatments for the purpose of eliminating pain, especially pain due to nerve damage (which is referred to as sympathetically mediated pains or SMP). These compositions contain as their principle and active therapeutic agent a drug from one (or more) of the following 3 classes of agents;

Class 1. The non-competitive n-methyl d-aspartate ion channel blocking agents, which will be referred to hereafter as NMDA receptor antagonists, such as ketamine (U.S. Pat. No. 3,254,124) and dextromethorphan (U.S. Pat. No. 2,676,177). Ketamine is currently used as a general anesthetic and primarily administered parenterally by injection. Dextromethorphan is used primarily as a cough suppressant.

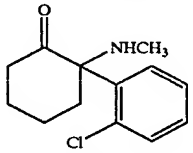
Class 2. The anticholinergic agents, an example of which are tricyclic antidepressants such as amitriptylline (U.S. Pat. No. 3,205,264). Amitriptylline is currently primarily prescribed for the oral treatment of depression. It is secondarily prescribed for use as an oral analgesic. It is also available parenterally.



Amitriptylline



Guanethidine



Ketamine

Class 3. Sympathetic blocking agents such as guanethidine. (U.S. Pat. Nos. 2,928,829, 3,006,913, and 3,055, 882) This group of drugs is currently generally prescribed for the treatment of peripheral vascular disorders and hypertension. These agents are available by both the parenteral and oral routes.

None of the agents in any of the above three classes is currently available nor prescribed for use by topical administration.

Preparation of Topical Compositions:

To prepare a topical composition, one or more of the active therapeutic agents from the three classes above is directly mixed with a suitable topical base. The efficacious and used most commonly base in our studies is a lecithin matrix gel. The efficiency of lecithin, a matrix base, is attributed to its ability to enhance transport of the active therapeutic agent across the dermis and into the tissues below so as to exert the effects of these agents on the nerves in the region below where it is applied.

The main ingredients used to make the matrix gel are pure soybean lecithin granules and liquid octylpalmatate. The liquid octylpalmatate and ground lecithin are mixed at room temperature in a proportion of 60% lecithin to 40% octylpalmatate. For example, 1 kilogram of lecithin is added to 600 cc of octylpalmatate. This mixture is then placed in a large commercial-type blender and blended together to the point where the whole mixture becomes liquefied. Even though granules of lecithin will still be seen floating around in the mixture, the whole mixture should appear to be in an almost total liquid state. This liquid is then transferred to 500 cc beakers which are placed on standard magnetic stirrers and allowed to stir at half speed undisturbed for 24 hours. At the end of the 24 hours the remaining lecithin granules will have completely liquefied, leaving a dark brown homogenous liquid of light oily texture.

The active therapeutic agent is then added to the liquid gel. For example, injectable ketamine, 50 mg per ml, is added to the lecithin gel. For every 90 ml of the now liquefied lecithin, 10 ml of ketamine is added. By weight, the added 10 ml of ketamine equals 500 mg, resulting in 500 mg of ketamine per 100 cc of the 0.5% topical composition.

The liquefied lecithin tends to thicken and gel when additional water or other liquid is added, a reverse of the expected effect. As the 500 mg of ketamine is commercially

US005962496A

United States Patent [19]

Cugola et al.

[11] Patent Number: 5,962,496

[45] Date of Patent: Oct. 5, 1999

[54] INDOLE DERIVATIVES AS NMDA ANTAGONISTS

[75] Inventors: Alfredo Cugola; Romano Di Fabio; Giorgio Pentassuglia, all of Verona, Italy

[73] Assignee: Glaxo Wellcome SpA, Italy

[21] Appl. No.: 09/086,522

[22] Filed: May 29, 1998

Related U.S. Application Data

[63] Continuation of application No. 08/619,510, Mar. 29, 1996, Pat. No. 5,760,059.

[30] Foreign Application Priority Data

Oct. 14, 1993 [GB] United Kingdom 9321221

[51] Int. Cl.[6] A61K 31/415; C07D 231/04

[52] U.S. Cl. 514/404; 514/253; 514/323; 514/380; 514/386; 514/414

[58] Field of Search 514/323, 380, 514/392, 404, 414, 386, 253, 339, 313

[56] References Cited

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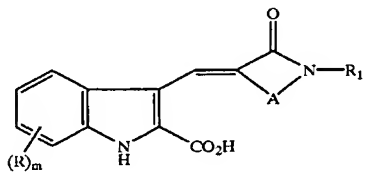
Primary Examiner—Joseph K. McKane

Attorney, Agent, or Firm—Bacon & Thomas PLLC.

[57] ABSTRACT

This invention relates to compounds of formula

(I)



or a salt, or metabolically labile ester thereof wherein R represents a group selected from halogen, alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, SO_2R_2 or COR_2 wherein R_2 represents hydroxy, methoxy, amino, alkylamino, or dialkylamino; m is zero or an integer 1 or 2;

R_1 represents a cycloalkyl, bridged cycloalkyl, heteroaryl, bridged heterocyclic or optionally substituted phenyl or fused bicyclic carbocylic group;

A represents a C_{1-4}alkylene chain or the chain $(CH_2)_pY(CH_2)_q$ wherein Y is O, S(O)n or NR_3 and which chains may be substituted by one or two groups selected from C_{1-6}alkyl optionally substituted by hydroxy, amino, alkylamino or dialkylamino, or which chains may be substituted by the group=O;

R_3 represents hydrogen, alkyl or a nitrogen protecting group;

n is zero or an integer from 1 to 2;

p is zero or an integer from 1 to 3;

q is zero or an integer from 1 to 3 with the proviso that the sum of p+q is 1, 2 or 3, which are antagonists of excitatory amino acids, to processes for the preparation and to other use in medicine.

8 Claims, No Drawings

strychnine insensitive glycine binding site associated with the NMDA receptor complex. As such they are potent antagonists of the NMDA receptor complex. Moreover the compounds of the invention exhibit an advantageous profile of activity including good bioavailibility. These compounds are therefore useful in the treatment or prevention of neurotoxic damage or neurodegenerative diseases. Thus the compounds are useful for the treatment of neurotoxic injury which follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospam, hypoglycemia, anaesia, hypoxia, anoxia, perinatal asphyxia cardiac arrest. The compounds are useful in the treatment of chronic neurodegenerative disease such as; Huntingdon's disease, Alzheimer's senile dementia, amyotrophic lateral sclerosis, Glutaric Acidaemia type, multi-infarct dementia, status epilecticus, contusive injuries (e.g. spinal cord injury and head injury), viral infection induced neurodegeneration, (e.g. AIDS, encephalopaties), Down syndrome, epilepsy, schizophrenia, depression, anxiety, pain, neurogenic bladder, irritative bladder disturbances, drug dependency, including withdrawal symptoms from alcohol, cocaine, opiates, nicotine, benzodiazepine, and emesis.

The potent and selective action of the compound of the invention at the strychnine-insensitive glycine binding site present on the NMDA receptor complex may be readily determined using conventional test procedures. Thus the ability to bind at the strychnine insensitive glycine binding site was determined using the procedure of Kishimoto H et al. J Neurochem 1981, 37 1015–1024. The selectivity of the action of compounds of the invention for the strychnine insensitive glycine site was confirmed in studies at other ionotropic known excitatory amino acid receptors. Thus compound of the invention were found to show little or no affinity for the kainic acid (kainate) receptor, a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor or at the NMDA binding site.

Compounds of the invention have also been found to inhibit NMDA induced convulsions in mice using the procedure Chiamulera C et al. Psychopharmacology (1990) 102, 551–552.

The neuroprotective activity of compounds of the invention may be demonstrated in the middle cerebral artery occlusion preparation in mice, using the procedure described by Chiamulera C et al. European Journal of Pharmacology 216 (1992) 335–336.

The invention therefore provides for the use of a compound of formula (I) and or physiologically acceptable salt or metabolically labile ester thereof for use in therapy and in particular use as medicine for antagonising the effects of excitatory amino acids upon the NMDA receptor complex.

The invention also provides for the use of a compound of formula (I) and/or a physiologically acceptable salt or metabolically labile ester thereof for the manufacture of a medicament for antagonising the effects of excitatory amino acids upon the NMDA receptor complex.

According to a further aspect the invention also provides for a method for antagonising the effects of excitatory amino acids upon the NMDA receptor complex, comprising administering to a patient in need thereof an antagonistic amount of a compound of formula (I) and/or a physiologically acceptable salt or metabolically labile ester thereof.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms.

It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 2 to 800 mg per day, dependent upon the route of administration.

Thus for parenteral administration a daily dose will typically be in the range 20–100 mg preferably 60–80 mg per day. For oral administration a daily dose will typically be within the range 200–800 mg e.g. 400–600 mg per day.

The desired dose may conveniently be presented in a single does or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a physiologically acceptable salt or metabilcially labile ester thereof together with one or more physiologically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant, or rectal administration. Parenteral administration is preferred.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions

US005234956A

United States Patent [19]

Lipton

[11] Patent Number: 5,234,956

[45] Date of Patent: Aug. 10, 1993

[54] METHOD OF PREVENTING NMDA RECEPTOR COMPLEX-MEDIATED NEURONAL DAMAGE

[75] Inventor: Stuart A. Lipton, Newton, Mass.

[73] Assignee: The Children's Medical Center Corporation, Boston, Mass.

[21] Appl. No.: 949,342

[22] Filed: Sep. 22, 1992

Related U.S. Application Data

[63] Continuation of Ser. No. 688,965, Apr. 19, 1991, abandoned.

[51] Int. Cl.[5] A61K 31/045

[52] U.S. Cl. 514/724

[58] Field of Search 514/724

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Primary Examiner—S. J. Friedman

Attorney, Agent, or Firm—Fish & Richardson

[57] ABSTRACT

Disclosed is a method for reducing NMDA receptor-mediated neuronal damage in a mammal by administering to the mammal a nitric-oxide generating compound, or a physiologically acceptable salt thereof, in a concentration effective to cause such reduction. Also disclosed is a method for reducing NMDA receptor-mediated neuronal damage in a mammal by administering to the mammal nitroprusside, nitroglycerin, or a derivative of one of those compounds, in a concentration effective to cause such reduction.

13 Claims, 1 Drawing Sheet

METHOD OF PREVENTING NMDA RECEPTOR COMPLEX-MEDIATED NEURONAL DAMAGE

This is a continuation of application Ser. No. 07/688,965, filed Apr. 19, 1991, now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to the treatment of nervous system disorders, particularly disorders mediated by the N-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor complex.

Glutamate has been implicated as a significant factor in the neurotoxicity associated with hypoxic-ischemic encephalopathy, anoxia, hypoglycemia, seizures, trauma, and several degenerative neurological disorders such as the AIDS dementia complex and other neurological manifestations of AIDS, Huntington's disease and Parkinsonism (Hahn et al., *Proc. Natl. Acad. Sci. USA* 85:6556, 1988; Choi, *Neuron* 1:623, 1988; Rothman et al., *Trends Neurosci.* 10:299, 1987; Meldrum et al., *Trends Pharm. Sci.* 11:379, 1990). In many central neurons the predominant form of this neurotoxicity appears to be mediated by activation of the NMDA subtype of glutamate receptor and subsequent influx of excessive Ca^{2+} (Choi, ibid; Weiss et al., *Science* 247:1474, 1990).

SUMMARY OF THE INVENTION

I have discovered that certain compounds protect neurons against NMDA receptor-mediated neuronal damage. Specifically, nitroglycerin, nitroprusside, and their derivatives provide such protection. Thus, one aspect of the invention features a method for reducing NMDA receptor complex-mediated neuronal damage in a mammal, by administering one of the above-described compounds to the mammal.

With regard to the compounds of the first aspect of the invention, I do not wish to bind myself to any particular theory or mechanism of action. However, oxidation of the NMDA receptor is known to protect against NMDA receptor-mediated neuronal damage (see, e.g., PCT W091/02180). It is also known that the active species of nitroglycerin and nitroprusside is nitric oxide (NO) (see, e.g., Garthwaite et al. (*Trends in Neurosciences* 14:60, 1991). Accordingly, one possible mechanism for the protective effect that I have discovered is nitric oxide-induced oxidation of the NMDA receptor-channel complex.

Accordingly, a second aspect of the invention features a method for reducing NMDA receptor complex-mediated neuronal damage by administering a nitric-oxide generating compound, in a concentration effective to cause such reduction. This second aspect of the invention is founded on the premise that NO acts on the NMDA receptor-channel complex to protect against NMDA receptor-mediated damage.

In preferred embodiments of both aspects of the invention, the mammal is a human infected with a virus affecting the nervous system—e.g., measles or human immunodeficiency virus (HIV); and the human manifests symptoms of the AIDS related complex or acquired immunodeficiency syndrome. Alternatively, the mammal has a disorder such as hypoxia, ischemia, hypoglycemia, trauma, seizures or stroke, or is likely to become subject to these, i.e., could be treated prophylactically.

By "NMDA receptor-mediated neuronal damage" is meant any neuronal injury which results from stimulation or costimulation of the NMDA receptor-channel complex, a receptor-channel complex which is found on a subset of mammalian neurons and which includes a molecule that interacts with NMDA or similar agonists (see below) to induce neuron excitation.

By a "nitric oxide-generating compound" is meant any compound which produces a sufficient amount of nitric oxide upon administration to a mammal to reduce neuronal damage or injury.

Useful compounds of the second aspect of the instant invention include any nitric oxide-generating compounds. Verification that a particular compound provides protective oxidation of the NMDA receptor itself is step well understood by those skilled in the art (see, e.g., PCT WO 91/02810). Moreover, applicant notes that the literature describes the enzyme, NO synthase, which produces nitric oxide in certain cell types; this enzyme and its role in neuronal function is discussed in, e.g., Garthwaite et al. (*Trends in Neurosciences* 14:60, 1991) and Hope et al. (*Proc. Natl. Acad. Sci. USA* 88:2811, 1991).

The two preferred compounds of the first aspect of the invention (i.e., nitroglycerin and nitroprusside) provide the advantage of a proven record of safe human administration (i.e., for treatment for cardiovascular disorders).

Disorders which may be treated by the method of the invention include hypoxia, ischemia, hypoglycemia, trauma, seizures, stroke, AIDS dementia and other neurological manifestations of HIV (see, e.g., U.S. Ser. No. 571,949) or other viruses affecting the nervous system, and, generally, acute and chronic neurodegenerative disorders, including, but not limited to Parkinson's disease, Alzheimer's disease, and Huntington's disease .

Regarding compounds according to the second aspect of the invention, the ability of NO to be transported and to cross cell membranes facilitates therapies according to the invention.

Other features and advantages of the invention will be apparent from the following detailed description and from the claims.

DETAILED DESCRIPTION

The drawings are first briefly described.

DRAWINGS

FIG. 1 is a bar graph showing that nitroprusside prevents NMDA-mediated neurotoxicity.

FIG. 2 is a bar graph of intracellular Ca^{2+} concentration (i.e., $[Ca^{2+}]i$) in (a) control cells and in the presence of (b) NMDA alone, (c) NMDA after dithiothreitol (DTT), and (d) NMDA after DTT and nitroprusside.

The present invention is based on the finding that the compounds nitroprusside and nitroglycerin reduce NMDA receptor complex-mediated neuronal damage (see below). This reduction in damage may be due to oxidation of the NMDA receptor at the redox modulatory site. The reduction is associated with a decrease in NMDA receptor-operated channel activation by excitatory amino acids (such as NMDA) and a concomitant decrease in intracellular calcium leading to neurotoxicity.

An increased level of one or more glutamate-related compounds is associated with many neurodegenerative disorders (e.g., those listed above). In addition to glutamate itself, neuronal injury may result from stimulation of the NMDA receptor-channel complex by other excitatory amino acids, such as aspartate, quinolinate,

United States Patent [19]

Cordi et al.

[11] Patent Number: 5,061,721

[45] Date of Patent: Oct. 29, 1991

[54] COMPOSITION CONTAINING D-CYCLOSERINE AND D-ALANINE FOR MEMORY AND LEARNING ENHANCEMENT OR TREATMENT OF A COGNITIVE OR PSYCHOTIC DISORDER

[75] Inventors: Alex A. Cordi, St. Louis, Mo.; Michel R. Jans, Brussels, Belgium

[73] Assignee: G. D. Searle & Co., Chicago, Ill.

[21] Appl. No.: 473,241

[22] Filed: Feb. 6, 1990

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 324,279, Mar. 15, 1989, abandoned.

[51] Int. Cl.[5] A61K 31/42; A61K 31/195

[52] U.S. Cl. 514/376; 514/561

[58] Field of Search 514/376, 561

[56] References Cited

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Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—J. Timothy Keane; Paul D. Matukaitis

[57] ABSTRACT

A composition is described for use in memory and learning enhancement or for treatment of a cognitive disorder or a psychotic disorder. This composition contains the compound D-cycloserine and D-alanine and provides reduced adverse side effects typically associated with chronic D-cycloserine use.

17 Claims, 2 Drawing Sheets

COMPOSITION CONTAINING D-CYCLOSERINE AND D-ALANINE FOR MEMORY AND LEARNING ENHANCEMENT OR TREATMENT OF A COGNITIVE OR PSYCHOTIC DISORDER

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. application Ser. No. 07/324,279 filed Mar. 15, 1989, now abandoned.

FIELD OF THE INVENTION

This invention is in the field of clinical neurology and relates specifically to compounds, formulations and methods for memory enhancement and for treatment of cognitive and psychotic disorders.

BACKGROUND OF THE INVENTION

There are many memory-related conditions for which therapeutic treatments are under investigation, such as methods to enhance memory or to treat memory dysfunction. For example, memory dysfunction is linked to the aging process, as well as to neurodegenerative diseases such as Alzheimer's disease. Also, memory impairment can follow head trauma or multi-infarct dementia. Many compounds and treatments have been investigated which can enhance cognitive processes, that is, which can improve memory and retention.

For example, the compound D-cycloserine has been discovered recently to provide improvements in cognitive function and to be useful in treatment of cognitive dysfunction, as described in U.S. Pat. application Ser. No. 07/127,121 filed Dec. 1, 1987, now U.S. Pat. No. 4,904,681 and application PCT/US88/04244 filed Dec. 1, 1988.

There are many psychotic states for which therapeutic treatments are under investigation. Drugs which are currently available on the market are thought to act as antagonists at the dopaminergic receptors located in the Central Nervous System (CNS), examples of such drugs being haloperidol and chlorpromazine. These drugs typically induce long lasting and sometimes irreversible side-effects, such as tardive dyskinesia. Thus, the search for improvements in therapy for psychotic disorders has been directed to use of drugs with a different mode of action.

Phencyclidine [1-(-phenylcyclohexyl)piperidine; PCP] is a known general anesthetic and is in use as an animal tranquilizer. PCP is a potent psychotomimetic agent used frequently as a "street" drug. Widespread abuse of PCP has led to increased incidence of PCP-induced psychoses [C. V. Showalter et al, *Amer. J Psychiat.*, 134, 1234 (1977)]. PCP abusers experience an apparent sensory isolation accompanied by a feeling of depersonalization which can be terrifying to the person. These subjective changes make PCP an appropriate drug model for study of schizophrenia. The most impressive evidence that PCP psychosis resembles schizophrenia is the fact that drug users have been mistaken by experienced psychiatrists for schizophrenics before obtaining the history of drug use [S. H. Snyder, *Nature*, 355–356 (1980)].

PCP has been reported to modulate allosterically the NMDA receptor [P. Loo et al, *Eur. J. Pharmacol.*, 467–468 (1986)] and it has been speculated that the psychotomimetic activity of PCP is related to its antagonism of NMDA transmission [C. A. Tamminga et al, Synapse, 1, 497–504 (1987)]. Facilitation of NMDA transmission by action at the glycine modulatory site may antagonize the effect of an endogenous PCP-like ligand [R. Quirion et al, *Peptides*, 5, 967–973 (1984)]. Also it has been postulated that glutamatergic action at the glycine-modulated NMDA receptor may be a route to treatment of schizophrenic [S. I. Deutch et al, *Clin. Neuropharm.*, 12, 1, 1–13 (1989)].

D-cycloserine has long been known as a bacteriostatic agent [see *The Merck Index*, Monograph No. 2747, 10th Edn., Merck & Co., p.395 (1983)]. Its mechanism of action is believed to involve inhibition of cell wall synthesis in susceptible organisms by competing with D-alanine for incorporation into the bacterial cell wall. Also, it is known that the in vitro antibacterial activity of D-cycloserine may be inhibited with D-alanine [Goodman & Gilman, *The Pharmacologic Basis of Therapeutics*, 7th Edn., MacMillan, N.Y., p. 1209 (1985)].

The compound D-cycloserine, in its D- and L-isomer forms, has also been evaluated for CNS effects in animals [O. Mayer et al, *Arzneim. Forsch.*, 21(2) , 298–303 (1971)]. These cycloserine isomers have also been evaluated for psychological and physiological effects in human subjects. For example, D-cycloserine when administered at 500 mg/day doses to healthy human subjects, appeared to stimulate slight sociability, but with depressed mental alertness [M. Vojtechovsky, *Act. Nerv. Super.*, 7(3) 269 (1965)]. Also, D-cyloserine has been administered at 1000 to 1500 mg/day to healthy volunteers whose blood levels showed increased levels of monoamine oxidase enzyme activity [V. Vitek et al, *Psychopharmacologia*, 7(3), 203–219 (1965)].

D-cycloserine has been investigated as a therapeutic agent for mental disorders in clinical trials, wherein D-cycloserine was administered to mentally disturbed patients at doses of 500 mg. per day [G. E. Crane, *Compr. Psychiat.*, 2, 51–53 (1961)]. In such clinical trials, improvements in depression, insomnia, anexoria or tension were found for some patients, while patients suffering from severe neurosis or psychosis responded poorly to such medication. Moreover, D-cycloserine has been used to exacerbate the symptoms of schizophrenia in an attempt to cure the ailment by symptom provocation [J. Simeon et al, *Compr. Psychiat.*, 11, 80–88, (1970)]. It appears that D-cycloserine, at the dose levels used in these studies, is acting as an antagonist at the glycine site of the NMDA-PCP receptor complex mimicking the action of PCP by inducing psychosis.

D-cycloserine has been sold commercially for treatment against Mycobacterium tuberculosis. When used at tuberculostatic doses, D-cycloserine is accompanied by many adverse side effects. The most frequent adverse side effects known involve the nervous system. In fact, the limiting factor in use of cycloserine is its CNS toxicity, including both neurologic and psychic disturbances [*Drug Evaluation*, Chapter 75, American Medical Association, Chicago (1986)]. Patients receiving D-cycloserine have been noted to suffer from drowsiness, dizziness, headache, lethargy, depression, tremor, dysarthria, hyperreflexia, paresthesia, nervousness, anxiety, vertigo, confusion and disorientation with loss of memory, paresis, major and minor clonic seizures, convulsions and coma [G. K. McEvoy et al, *American Hospital Formulary Service: Drug Information*, 8:16, American Society of Hospital Pharmacists, Bethesda, Md. (1986)].

US005162311A

United States Patent [19]

Herrling et al.

[11] Patent Number: 5,162,311

[45] Date of Patent: Nov. 10, 1992

[54] α-AMINO-α(3-ALKYL-PHENYL)ALKYL ETHANOIC ACIDS WHEREIN THE 3-ALKYL MOIETY BEARS A PHOSPHORUS OXO ACID GROUP OR AN ESTER THEREOF, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

[75] Inventors: **Paul L. Herrling**, Berne; **Werner Müller**, Gümligen, both of Switzerland

[73] Assignee: **Sandoz Pharmaceuticals Corp.**, E. Hanover, N.J.

[21] Appl. No.: **747,177**

[22] Filed: **Aug. 19, 1991**

Related U.S. Application Data

[63] Continuation of Ser. No. 499,155, Mar. 26, 1990, abandoned, which is a continuation of Ser. No. 114,881, Oct. 29, 1987, abandoned.

[30] **Foreign Application Priority Data**

Oct. 30, 1986 [GB] United Kingdom 8625941

[51] **Int. Cl.**[5] **C07F 9/38**; C07F 9/40; A61K 31/66

[52] **U.S. Cl.** **514/110**; 514/114; 514/119; 554/84; 558/83; 558/190; 560/29; 560/30; 560/31; 560/32; 560/33; 560/38; 560/39; 560/41; 562/11; 562/15

[58] **Field of Search** 260/403; 562/11, 15; 558/83, 190; 514/110, 114, 119; 554/84

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Applicants were provided with copies of reference in Ser. No. 07/499,155.

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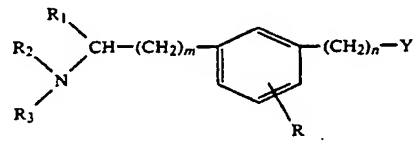
Primary Examiner—Robert T. Bond

Assistant Examiner—Jyothsna Venkat

Attorney, Agent, or Firm—Gerald D. Sharkin; Robert S. Honor; Joseph J. Borovian

[57] **ABSTRACT**

The invention discloses certain substituted α-aminoacids having the formula



where m and n are 1 or 2, and R, R_1, R_2, R_3 and Y have various significances, which compounds are useful in treating epilepsy, disorders associated with excess GH or LH secretion, anxiety, schizophrenia, depression, CNS degenerative disorders, cerebral hypoxic conditions and stress-related psychiatric disorders.

4 Claims, No Drawings

evaluate recovery. The values obtained in such experiments are again fed into the computer which plots bar-diagrams, calculates the means of the control-, drug- and recovery groups and tests statistically the difference between control and drug group. If a test drug shows inhibition in the first stage, competitive antagonism is tested in the second stage. This is done by determining a four point DRC of the agonist in the linear range and then repeating the DRC in presence of the putative antagonist at a constant concentration. Recovery is tested by repeating the DRC after the washout of the test drug. A first indication of competitive antagonism is given by a parallel shift to the right of the DRC in presence of the antagonist, e.g. compounds of the present invention at a concentration from 100 nM/l to about 300 μM/l, e.g. 1 to about 300 μM/l. In such cases pA_2-values are calculated according to the formula

$$pA_2 = -\log I + \log\left(\frac{A50}{B50} - 1\right)$$

where I is the concentration of the antagonist, A50 is the EC_{50} for the agonist in presence of the antagonist and B50 the EC_{50} of the agonist alone before the application of the test drug. Competitive antagonism can be confirmed by repeating the experiment with a double dose of the test drugs, if approximately the same pA_2 results there is a reasonable certainty that the antagonist is competitive (O. Arunlakshana et al., Brit.J.Pharmacol. 19, 48-58 (1959); M. Wenke, Drug receptor interactions. In BACQ ZM (ed) Fundamentals of biochemical pharmacology, Pergamon Press, Oxford, 357-381 (1971).

The compounds of the invention are also selective as indicated in that quisqualate induced depolarizations are not significantly effected in the above test wherein NMDA is replaced by quisqualic acid.

As a result of their NMDA receptor antagonism the compounds are useful in inhibiting GH and LH secretion and therefore useful i) in the treatment of disorders having an etiology comprising or associated with excess GH-secretion e.g. in the treatment of diabetes mellitus and angiopathy as well as of acromegaly and ii) in the treatment of disorders having an etiology associated with or modulated by excess LH-secretion e.g. in the treatment of prostate hypertrophy or in the treatment of menopausal syndrome. For these indications, the appropriate dosage will, of course, vary depending upon, for example the compound of the invention employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general for both uses i) and ii) above satisfactory results in animals are indicated to be obtained with a daily dosage of from about 0.01 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 800 mg, e.g. from about 1 to about 600 mg of a compound of the invention conveniently administered, for example, in divided doses up to four times a day.

As a result of their NMDA receptor antagonism the compounds of the invention are further useful in the treatment of anxiety, schizophrenia and depression or of CNS degenerative disorders, such as Huntington's, Alzheimer's or Parkinson's diseases. For these indications, the appropriate dosage will, of course, vary depending upon, for example, the compound of the invention employed, the host, the mode of administration and the nature and severity of the condition being treated.

However, in general, satisfactory results in animals are indicated to be obtained with a daily dosage of from about 0.5 to about 30 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 25 to about 800 mg, e.g. from about 25 to about 600 mg of a compound of the invention conveniently administered, for example, in divided doses up to four times a day.

The compounds of the invention protect further against hypoxia-induced degeneration of rat hippocampal neurons in vitro at concentrations ranging from 1 μM to 3 mM [method of S. Rothman, J.Neurosci. 4, 1884-1891 (1984)]. The compounds are therefore useful in the treatment of cerebral hypoxic/ischaemic conditions, e.g. stroke. For this indication the appropriate dosage will, of course, vary depending upon, for example, the compound of the invention employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.2 to about 10 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 10 to about 800 mg of a compound of the invention conveniently administered, for example, in divided doses up to four times a day.

Furthermore, the compounds of the invention inhibit plasma corticosterone rise, which is induced by social stress in mice. This can be shown in the following test:

One day before the experiment a group of 5 male mice (40-50 g, OF-1, Sandoz,Basle) were placed in a transparent makrolon cage Typ 3, which is cut in halves by a grid. The next day each mouse was given an oral dose of 0.3-30 mg/kg of a compound of the invention. Two hours later an isolated male mouse was introduced for 15 minutes into the empty half of the cage and two trained observers recorded the behavior of the mice in terms of acts such as dig, push-dig and rattle. Blood plasma samples were then taken from the tested mice group and assayed for corticosterone concentrations using a modified method of Paerson-Murphy B.E., J.Clin.Endocrinology 27 (1967) 973-990. The procedure was repeated with a control group of 5 mice which was given only a solvent.

As a result of their ability to inhibit plasma-corticosterone rise the compounds of the invention are useful in the treatment of stress-related psychiatric disorders, e.g. where the treatment of social withdrawal, which is present in many psychiatric disorders, e.g. schizophrenia, depression, generalized anxiety or in affective disorders, e.g. adjustment disorders with social withdrawal or anxiety, and other stress-related illnesses is desired. For this indication the appropriate dosage will, of course, vary depending upon, for example, the compound of the invention employed, the host, the mode of administration and the nature and severity of the condition to be treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.3 to about 30 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 800 mg of a compound of the invention conveniently administered, for example, in divided doses up to four times a day.

In the electroshock-induced convulsion test the Example 1 compound has an ED_{min} of <50 mg/kg i.p. As

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[54] METHOD FOR TREATING AND PREVENTING NEURODEGENERATIVE DISORDERS BY ADMINISTERING A THIAZOLIDINONE

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[58] Field of Search 514/369

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[57] ABSTRACT

Neurodegenerative disorders, i.e., Alzheimer's disease, stroke, multiple sclerosis and head trauma are treated with 5-[[{3,5-bis(1,1,-dimethylethyl)-4-hydroxyphenyl] methylene]-2-imino-4-thiazolidinone or a pharmaceutically acceptable salt thereof.

5 Claims, No Drawings

solutions were prepared in PBS and injected intraperitoneally (0.05 mL volume) 15 minutes, and 2.25 hours after intrastriatal injection of NMDA. Control animals received equal volumes of PBS.

After surgery, all animals were returned to the mothers for 5 days, and decapitated on PND 12. The brains were removed, the cerebral hemispheres were separated, and wet weights of each hemisphere were determined individually. Differences of the hemispheric weights were compared for each animal using the formula: 100×(C−I/C)=percent damage, a value that indicates the severity of damage of the injected (I) cerebral hemisphere relative to that of the uninjected contralateral (C) hemisphere. Percent protection is used to indicate the relative protection of the neuroprotective compound compared to the control and was calculated as: $100\times[1-(\%\ damage_{treated}/\%\ damage_{control})]$. Data were expressed as mean percent damage±S.E.M. in all groups. Independent t-tests were used for statistical comparisons. Previous experiments demonstrated that hemispheric weights correlated closely with reductions in both choline acetyltransferase activity and regional cross-sectional areas inspected histologically (α^2=0.99, p<0.001, linear regression). This same study also showed that intrastriatal PBS injections do not cause significant damage.

RESULTS

NMDA (15 nmol/0.5 μL) injected into the posterior striatum produced a 20.6±1.8% (N=10) reduction in the wet weight of the cerebral hemisphere ipsilateral compared to control animals that were given an intraperitoneal injection of PBS. All control animals survived to PND 12. The thiazolidinone, at the doses of 2×10 and 2×30 mg/kg, significantly prevented NMDA-induced injury (28.1±9.2% and 49±8.2%, respectively; p<0.04 and p<0.001). One animal dosed with thiazolidinone (2×30 mg/kg) did not survive to PND 12. Protection at the 2×30 mg/kg dose was comparable to that provided by the 2×30 mg/kg of indomethacin.

Over-activation of excitatory amino acid neurotransmission, especially that mediated by the NMDA receptor, is responsible for much of the neuronal damage resulting from cerebral ischemia, such as that found following a stroke or neural trauma. The fact that the thiazolidinone ameliorates NMDA-induced injury thus establishes that it is useful in treating neuronal injury resulting from cerebral ischemia.

EXAMPLE 2

The thiazolidinone was evaluated in a mouse model of experimental autoimmune encephalomyelitis (EAE). The compound was administered orally to mice sensitized with a fragment of mouse myelin basic protein to induce EAE. Two experiments were conducted using the same protocol and neurological evaluations. Test animals were dosed for 21 days, beginning 4 hours before sensitization on Day 1. The effects of the thiazolidinone were compared to a control group of mice sensitized identically and dosed with vehicle alone. Neurological evaluations continued after cessation of drug treatment. The values reported in Tables 1 and 2 below include responses during drug treatment only.

Drug Preparation and Treatments

The thiazolidinone was homogenized manually with an aliquot of warm vehicle (0.5% hydroxypropyl methylcellulose with 0.2% Tween 80in water) in glass mortar tubes and homogenizing pestle. The smooth drug paste was gradually suspended in vehicle. Mice were dosed with drug and/or vehicle, 10 mg/kg in groups of ten (Experiment 1) or twenty (Experiment 2). Mice were dosed from Experiment Day 1 to Day 21. A sham-sensitized group was similarly dosed with vehicle or thiazolidinone 30 mg/kg (Experiment 1).

Sensitization

Female mice, strain PL/J(F1)×SJL/J from Jackson Labs, were sensitized s.c. (0.05 cc×2) at the base of the tail with an emulsion containing equal parts of mouse myelin basic protein (MBP) fragment (amino acids 1–9 of the N-terminus of MBP) in saline and Difco Complete Freund's Adjuvant (CFA) fortified with heat killed desiccated *Mycobacteria tuberculosis* (MT). Each mouse received 300 μg of the MBP fragment (230 μg free base) and 200 μg MT followed by retrobulbar (i.v.) injection of 200 ng of *B. pertussis* toxin in 0.2 cc of saline. Forty-eight hours later, mice received a second injection of *B. pertussis* toxin. Mice in Experiment 1 were 8 to 9 weeks old; mice in Experiment 2 were 11 weeks old.

Neurological Assessment

Animals were weighed and evaluated for symptoms of EAE before sensitization and frequently for 21 days. EAE score: (0.5=slight limp tail, 1=limp tail or slow to right, 1.5=slight limp tail and slow to right, 2=paresis/mild paralysis or incontinence, 2.5=mild paralysis and slow to right or complete paralysis (one hind limb), 3=hind limb paralysis (both), 3.5=hind limb paralysis (both) and limp torso; 4=additional fore limb paralysis, 4.5=head movement only, 5=moribund, death after previous EAE symptoms). Evaluators were blinded as to drug treatments and previous behavioral scores.

Disease symptoms were compared among groups for EAE severity, incidence, time to onset, cumulative score, deaths, and weight loss. Peak EAE score: the mean of highest score of each mouse in a group, independent of duration of symptoms; EAE incidence: the mean number of mice showing symptoms of EAE, defined as having EAE scores on any three consecutive days that total≧3.0. EAE deaths: An animal that died must have presented previous evidence of an EAE score greater than 0.5; EAE onset: the first of a 3-day series scoring a total of≧3.0. A Cumulative EAE score is calculated for each animal. A mean of all animals' cumulative score is then determined for each day. Maximum weight loss: the mean of the lowest weight for each animal in a group. (Note: The Cumulative EAE score and the Maximum weight loss can be influenced by death which eliminates severely diseased animals. The number of days that animals are scored also affects the cumulative score and can only be compared "within-trial"). Mice that die from dosing trauma or with no previous symptoms of EAE are deleted from the study. Experimental groups were assumed to be similar and were compared for statistical significance by a two-tailed t-test (p≦0.05).

RESULTS

Experiment 1

The sensitized vehicle controls exhibited robust symptoms of EAE, as shown by the daily EAE score and a spectrum of neurological criteria (Table 1). The control group had 3/10 EAE deaths, while sham-sensitized mice treated with vehicle or thiazolidinone 30 mg/kg group